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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,462	12/06/2001	Aillette Mulet Sierra	3159-9230US	4354

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
03/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/003,462	SIERRA ET AL.	
	Examiner	**Art Unit**	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _01 October 2008_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1,2,4-7,12-18 and 20-24_ is/are pending in the application.

4a) Of the above claim(s) _14-18_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1, 2, 4-7, 12, 13 and 20-24_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Clams 1, 2, 4-7, 12-18 and 20-24 are pending. Claims 14-18, drawn to non-elected inventions, are withdrawn from consideration. Claims 1, 2, 4-7, 12, 13 and 20-24 are examined on the merits.

Claim Rejections Maintained and New Grounds of Rejection:

Claim Objections

Claim 2 is objected to because of the following informalities: a typographical error "fwherien". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4-7, 12, 13 and 20-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 11, 12, 13, 14, 18-25, 29, 33-38, 40-52, 56-59, 61, 65 and 66 of copending Application No. 11/407,103. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and methods of treatment claims of copending application no. 11/407,103 recite a composition that comprises a vaccine directed against TGF-alpha, where the TGF-alpha is coupled to a carrier protein such as P64K. A preferred embodiment appears to be human TGF-alpha, because the specification teaches and example of the use of TGFalpha as a vaccine for making ligand blocking antibodies for use in patients (see page 4, line 19 – page 5, line 21).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Claim 23 is drawn to a composition comprising the amino acid sequence of SEQ ID NO: 2 coupled to P64k, together with adjuvant, wherein the composition is able to produce a specific

immune response in a subject against hTGFalpha, wherein the ratio of the adjuvant to the hTGFalpha is about 3 to 1 by weight. Claim 24 recites the limitation that the ratio of the adjuvant to the hTGFalpha is about 40 to 1 by weight. The limitations of the ratio of the adjuvant to hTGFalpha is a new limitation that was not present in the claims as originally filed. In the amendment filed 10/1/2008, applicants have not specifically pointed to support for these new limitations. After a review of the specification, while various examples of compositions with having different doses of hTGFalpha and different amounts of adjuvant can be found, there does not appear to be support for the specific ratios as recited in the claims. Therefore, new claims 23 and 24 introduce new matter into the specification as originally filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7, 12, 20 and 21 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999) and further in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994) for the reasons of record. This rejection is applied to new claims 20 and 21.

Hoeprich teaches compositions where the hTGFalpha is present at 50-200 micrograms per dose (see page 19087, left column). Thus, Hoeprich teaches compositions that meet the dosage limitations of claims 20 and 21.

Applicants assert that no motivation exists to combine the prior art elements in the manner presently claimed, that the references teach away from the claimed composition, and no reasonable expectation of success would have existed for combining the prior art in the manner claimed. Applicants state that Davila teaches EGF conjugated to a laundry list of types of carrier proteins such as tetanus toxoid, Cholera toxin B (CTB) chain or P64; and that Davila teaches that the carrier protein CTB achieved the best results and is expressly preferred as a carrier protein with EGF. Applicants conclude that Davila provides motivation for using CTB as a carrier

protein rather than P64k. Applicants further assert that the claims are not obvious as none of the references relied upon by the office teach or suggest that a combination of hTGFalpha and P64k would be effective in producing a specific response against hTGFalpha; and that it is understood in the art that the development of vaccines against a specific antigen target is a highly complex and specific process; and that while Davila may teach that P64k can be used with EGF, there is not reasonable expectation that hTGFalpha would be effective with P64 in eliciting a specific immune response; and that Hoeprich suggests as much, stating that although TGFalpha and EGF share some sequence homology (33-40%), "their antibodies do not cross react, and they differe significantly in their occurrence"

Applicants' arguments have been carefully considered, but fail to persuade. With respect to applicants' argument that Davila provides a teaching away from using P64k as a carrier protein because Davila shows that CTB conjugated to EGF is more effective that P64k conjugated to EGF, this is not found to be a "teaching away" because P64k was not shown to be inoperable, merely not as good as CTB. When combined with applicants' next argument that results with EGF cannot be used to predict a result with hTGFalpha, applicants' argument appears to be weakened further because if one accepts the proposition that one cannot extrapolate from teachings concerning EGF conjugation to an expectation of success for hTGFalpha conjugation, then it does not follow that Davila leads one to choose CTB when attempting to find a useful carrier protein for hTGFalpha. Thus, applicants' assertion that Davila provides a "teaching away" from the claimed invention is not persuasive. As stated in the previous Office action, Davila teaches that P64k is a useful carrier protein. The situation presented in the rejection over the combination of Hoeprich, Davila and Rodriquez appears to be similar to one

discussed in KSR Int'l Co. v Teleflex Inc. 550 U.S.-, 82 USPQ2d 1385 (2007) "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." KSR at 1395 (citing United States v. Adam, 383 US39, 50-51 (1966)). In the present case, Hoeprich provides hTGFalpha conjugated to keyhole limpet hemocyanine in combination with Freund's complete adjuvant or Freund's incomplete adjuvant. The component that needs to be substituted is the carrier protein because Hoeprich teaches keyhole limpet hemocyanine as a carrier protein instead of P64k as a carrier protein. However P64k is a component known in the art as evidenced by Davila, which teaches it conjugated to EGF as a carrier protein. The teachings of Rodriquez provide evidence that the P64k was a protein in the public domain at the time the invention was made, and known to have immunogenic properties in humans. Therefore, one of ordinary skill in the art could have substituted the keyhole limpet hemocyanine carrier protein of Hoeprich with the P64k protein of Davila (or of Rodriquez, which provides the amino acid sequence), because Davila teaches its use as an immunogenic carrier protein. Contrary to applicants' assertion that Davila provides a laundry list of possible carrier proteins, Davila shows three examples, of which P64k is one. Thus, Davila presents a finite number of possible carrier proteins. Because the sequence of P64k was known, and because Davila provides a method for making EGF conjugates, it would have been within the grasp of the ordinary artisan to make different hTGFalpha conjugates, including an hTGFalpha - P64k conjugate with a reasonable expectation that such a conjugate would be immunogenic, because Davila's EGF-P64k conjugate was immunogenic and because Hoeprich's hTGFalpha-heyhole limpet hemocyanine conjugate was immunnogenic. Therefore, the rejection is maintained for the reasons of record.

Claims 1, 2, 4, 5, 7, 12, 13, 20 and 21 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999), in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994), and further in view of Gonzalez-1997 (of record). This rejections is applied to new claims 20 and 21.

The claims encompass vaccine compositions comprising fusion proteins, where hTGFα is fused with P64k. Applicants request withdrawal of the rejection under 35 USC 103(a) on the same grounds as argued above for the previous rejection. However, for the reasons given above, the rejection is maintained for the reasons of record.

Claims 1, 2, 4-7, 12, 13, 20 and 21 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999), in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994), in view of Gonzalez-1997 (of record), and further in view of Ritzenthaler (Ritzenthaler, C. et al., J. General Virology, 76: 907-915, 1995) for the reasons of record.

The claims encompass vaccine compositions comprising fusion proteins, where hTGFα is fused with P64k, and wherein the expression vector of bacteria presents a genetic sequence coding for six histidines. Applicants request withdrawal of the rejection under 35 USC 103(a) on the same grounds as argued above for the previous rejection. However, for the reasons given above, the rejection is maintained for the reasons of record.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 14, 2009
/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643